1 Critical Care Versus Critical Illness

Patrick J. Neligan, Clifford S. Deutschman

Intensive care units (ICUs) were developed in the 1950s to treat patients with two distinct problems. In some cases, ICU care was required to provide an intervention to support organ dysfunction—mechanic ventilation for acute respiratory failure.[1,2] Conversely, ICUs also permitted intensive monitoring of a patient whose physiologic condition might change abruptly, that is, observation of patients undergoing a "stress response" following surgery or trauma or patients with cardiac or neurologic conditions that might suddenly change.[3,4] Over time, technologic evolution has enhanced our ability to care for both types of patients. In addition to ventilators, it is now possible to support patients with life-threatening, acute organ dysfunction with renal replacement therapy, vasoactive drugs or even ventricular assist devices, exogenous metabolic support, and more. At the same time, we can directly monitor the function of areas such as the heart, the lungs, the brain, the gastrointestinal (GI) tract, and the kidneys. Over the years, the distinction between the two forms of technology has blurred: we monitor patients who require life-sustaining therapy, and we support organs in patients who are at high risk to prevent deterioration. The difference between the two types of patients remains. There are patients who will most often have a predictable response to a major perturbation of homeostasis following high-risk (e.g., cardiac, neurologic, vascular, transplant, and upper GI) surgery, trauma, a myocardial infarction (MI) or arrhythmia, stroke, or subarachnoid hemorrhage. These patients may require intervention to allow the damage to heal, but, by and large, they require careful monitoring and observation as they traverse a course whose length, magnitude, and complications are predictable.[5,6] Conversely, patients who have sustained shock, sepsis, or direct/progressive damage to an organ system require support, and monitoring is used to determine if that support is working. In short, there are ICU patients who are at risk of becoming critically ill, and there are patients who *are* critically ill (Fig. 1-1). In this introductory chapter, we explore the differences and emphasize that the most important tasks facing modern medicine are to determine where the transition occurs and to prevent those at risk for critical illness from becoming critically ill.

THE PERIOPERATIVE/POSTINJURY STRESS RESPONSE

In contrast to critical illness, the biology underlying the stress response to surgery or trauma is well-characterized, predictable, and, absent comorbidities that may be effected, adaptive.[5,6] Cuthbertson first described the stress response over 80 years ago.[5] Since then, a number of brilliant investigators and clinicians have added to our understanding of its biology.[7-9] We now recognize that "stress" provokes inflammation and that the purpose of inflammation is restoration of a biologic "steady state," where cellular, tissue, organ system, and, ultimately, organism-wide activity fluctuates around some mean level of behavior and maintenance of interaction and cooperation on these same levels.[6] In most cases, the overwhelming imperative driving inflammation is a need to repair, replace, or compensate for damage to cells and tissues.[6] This damage may result from physical injury (trauma), from interruption of blood supply (e.g., stroke, MI), or from invasion of microorganisms that "hijack" normal cellular metabolism.

CRITICAL ILLNESS

Critical illness is characterized by acute, potentially life-threatening organ dysfunction that requires therapy. It is often precipitated by the same disturbances that provoke inflammation. The initiator may be "shock," whose origin can often, but not universally, be traced to circulatory failure or to infection that overwhelms endogenous responses. The common denominator is a profound insult to homeostasis on the cellular level that exceeds endogenous corrective responses. However, the manner in which these states result in abnormal organ function is unknown.

Critically ill patients may present to primary care, to the emergency department (ED), or on the hospital wards. They represent a small subset of patients; the vast majority of individuals with deviations from "health," for example, those with inflammation or even shock, respond to initial therapy. A few, however, become acutely critically ill. Acute critical illness is often unanticipated and may not follow a predictable stress response trajectory.

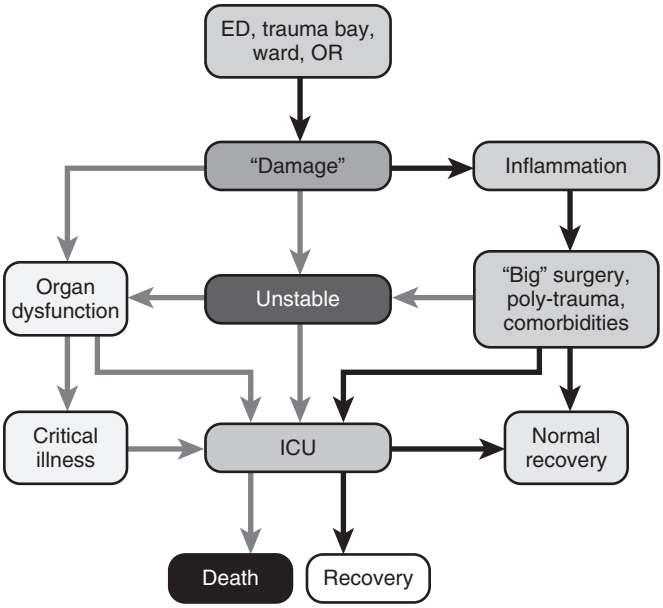

Figure 1-1 The critical care–critical illness paradigm. *ED*, emergency department; *ICU*, intensive care unit; *OR*, operating room.

With early recognition and appropriate therapy, many critically ill patients will recover. Once again, however, a subset will deteriorate further, to a state of *persistent critical illness* with multiorgan dysfunction (see Chapter 37). This state may persist for weeks and thus can appear stable, but it is also highly abnormal, with defects in most organ systems.[10,11] Once again, many patients will recover. However, it is increasingly clear that this recovery is incomplete. Many patients who have undergone a prolonged ICU course are left with persistent respiratory, cardiac, neuromuscular, and cognitive dysfunction.[12-15] Some may remain ventilator dependent; others will have a variant of posttraumatic stress disorder.[13] Recent studies suggest that, in the United States, there may be upward of 700,000 ICU survivors each year, many of whom require ongoing support, but many others whose ongoing problems escape detection.[16]

INFLAMMATION VERSUS CRITICAL ILLNESS: BIOLOGIC PERSPECTIVES

Both inflammation and critical illness are, at the core, responses to significant, and often extreme, perturbation of homeostasis, the biologic steady state. As a result, there is a tendency to assume that therapy appropriate for one will also be effective for the other. There is, indeed, some truth to this assumption. As an example, in both inflammation and critical illness, an initial imperative is the restoration of substrate delivery to and waste removal from cells. However, the profound change that differentiates inflammation from critical illness has been characterized by some as a loss of a cell's ability to use substrate, or the creation of a by-product that cannot be removed by ordinary means. Consider the cellular need for oxygen. Inadequate delivery may reflect abnormalities in the lungs, with impaired gas exchange, or in the circulation, where the cardiovascular system is unable to transfer oxygen itself, or oxygen-containing molecules or cells, to tissues for use. Cells can often meet energy demands by means of glycolysis alone, bypassing the electron transport chain, and generating lactate and hydrogen ions. Recycling of lactate requires an intact circulation for delivery to the liver. Acidosis is corrected by buffering with the production of carbon dioxide (CO_2), which must be excreted by ventilation. Thus, a clinician's initial response would be to enhance oxygen uptake by increasing the inspired concentration, restoring the circulation with fluid, and, perhaps, increasing the oxygen-carrying capacity with red blood cells. This same fluid will restore hepatic flow and allow for the conversion of lactate to pyruvate. Improving gas removal with mechanical ventilation will facilitate CO_2 removal. This approach may be effective when directed toward inflammation secondary to tissue damage, where oxygen use is diverted to support white blood cells, the primary effectors of tissue repair, and where delivery is inadequate because damaged tissue is essentially avascular. This response is self-limiting because capillary angiogenesis takes about 4 days,[17] after which exogenous support can be weaned. However, a more profound insult, or one that is not addressed in a timely manner, may do more than limit oxygen availability or divert its use. Damage to mitochondria, which is a hallmark of sepsis, will impair the ability of a cell to use oxygen irrespective of availability.[18,19] Thus, restoration of gas exchange or cardiovascular function will not, in and of itself, be sufficient to restore homeostasis. As a result, organ dysfunction may not improve or resolve with these standard measures—a hallmark of critical illness that is often unrecognized or unappreciated. Unfortunately, the distinction between stress and critical illness is not always clinically self-evident, and this lack of distinction leads to diagnostic and therapeutic dilemmas whose resolution, for the moment, is intensely problematic.

INFLAMMATION VERSUS CRITICAL ILLNESS: THERAPEUTIC PERSPECTIVES

An unfortunate extension of our difficulties in distinguishing a stress response from critical illness is a persistent tendency to assume that what works for one group will also work for the other. Examples abound. The following is a summary of several of the most important examples, both historically and therapeutically:

- *Fluid resuscitation in sepsis*: In a landmark 2001 study by Rivers and colleagues,[20] researchers studied patients with suspected infection who were thought to have sepsis and compared fluid resuscitation using standard endpoints such as blood pressure (BP) to alternatives that focused on tissue oxygen delivery, for example, venous oxygen saturation (SvO_2) or central venous pressure (CVP). This single center study demonstrated a remarkable improvement in outcome using the latter approach. However, three recent multicenter studies applying essentially the same paradigm failed to duplicate the original findings.[21-23] A number of possible explanations have been advanced, but it is essential to note that in "inflammation," adequate resuscitation may be

reflected in measures such as CVP and SvO_2. However, sepsis involves a pathologic defect in either the microcirculation or the mitochondria so that oxygen delivery or extraction cannot be corrected with fluid alone.[18,24] Unfortunately, the entry criteria in both the initial Rivers trial and the subsequent multicenter trials cannot truly distinguish inflammation and hypovolemia secondary to suspected infection for sepsis, a state of critical illness that reflects early organ dysfunction that is difficult to detect. Fluid resuscitation that is appropriate for one may be ineffective, and even excessive, for the other.

- *Ventilator management in acute lung injury/acute respiratory distress syndrome (ARDS)*: A series of studies by a network of United States–based investigators and others have examined therapeutic approaches to lung injury. The most important of these "ARDSnet" studies is the initial "ARMA" trial, demonstrating that limiting tidal volumes to 6 cc/kg body weight is associated with better outcomes than use of larger (10 to 12 cc/kg) volumes.[25] The diagnosis of ARDS was based on the standard criteria: hypoxemia, reflected in a decreased ratio of arterial oxygen tension (Pao_2) to fraction of oxygen in the inspired gas (Fio_2), the presence of bilateral "patchy" infiltrates on chest radiographs, and no evidence that the abnormalities were of cardiogenic origin. Conversely, for decades, anesthesiologists have administered tidal volumes in the 10 to 12 cc/kg range in the operating room. Many, if not most, postoperative patients have abnormal Pao_2/Fio_2 ratios and abnormal chest radiographs. This is especially true for patients undergoing cardiac surgery. Postoperatively, though, the great majority of these patients do not require more than supplemental oxygen. Even in those who are maintained with mechanic ventilation into the postoperative period, exogenous support is rarely needed for more than a short period. All surgical patients have capillary leak as part of the inflammation induced by tissue injury. This "stress response" results in mild hypoxemia and "wet" lungs. In contrast, patients with ARDS have lung dysfunction. Postoperative patients have inflammation; patients with ARDS have critical illness.
- *Determination of outcome*: The management of patients with sepsis has been an important focus of critical care practice for more than a decade.[26-28] Attempts to consolidate limited positive multicenter clinical trials in critical care have resulted in international and national clinical practice management guidelines. Perhaps the most widely disseminated involve the Surviving Sepsis Campaign (SSC) guidelines for the management of sepsis. The SSC (www.survivingsepsis.org) has been effective in increasing awareness of early sepsis and perhaps in advancing the implementation of therapy that may improve outcome.[29] Importantly, recent studies from the United States and Australasia have demonstrated that mortality from sepsis has decreased to surprisingly low levels—under 10% in one multi-institutional U.S. health system[30] and under 20% when more broadly applied over a 12-year period in Australia and New Zealand.[31] However, personal communications from intensivists in the three industrialized European countries suggest that, despite use of some or all elements of the SSC guidelines, mortality may be as high as 50% (personal communications, Mervyn Singer, M.D.). The expressed opinion of those practicing in the United Kingdom, Germany, and Italy is that many patients diagnosed with sepsis and admitted to ICUs in the United States and Australasia would be managed in the EDs of other countries. If these patients responded to ED management, they would not be admitted to the ICU and would not be identified as "septic." To further complicate matters, Gaieski et al.[32] applied four different methods of defining "sepsis" to a single U.S. patient dataset and found a 3.5-fold variation in the incidence and a 2-fold variation in mortality. Clearly, some of the patients diagnosed with sepsis in the United States and Australasian databases were undergoing inflammation in response to infection. Again, differentiating inflammation from critical illness is profoundly important.
- *Intensive insulin therapy*: In 2001, Van den Berghe and colleagues[33] published a much sited clinical trial that randomized patients to *intensive insulin therapy* (ITT) (glucose levels maintained between 80 and 110 mg/dL), as opposed to "normal care" (glucose levels treated when above 180 mg/dL). The study was based on the knowledge that hyperglycemia is associated with a number of untoward outcomes in critically ill patients and demonstrated a statistically significant 3.4% absolute reduction in the risk of death at 28 days in the surgical ICU of a major hospital in Leuven, Belgium. The paucity of interventions that improve outcomes in critical care and the fact that insulin is inexpensive and easy to administer led to wide adoption of ITT. Although Van den Berghe et al.[33] clearly documented the need for careful monitoring of blood glucose levels and the risk of hypoglycemia, these potential complications were largely ignored. "Tight glycemic control" was even considered a key performance indicator in many ICUs[34] and became a component of the first SSC guidelines.[26] However, some elements of the study methodology suggested that the near-universal adoption of IIT might be problematic. Specifically germane to this discussion is the fact that more than 60% of the patients who entered into the study had recently undergone cardiac surgery, and virtually all were seen either postoperatively or posttraumatically. A follow-up study by the Van den Berghe group[35] applied the same protocol to patients in the medical ICU of the same institution and failed to demonstrate outcome benefits. In addition, somewhat problematic trials were stopped early because of concerns that high levels of hypoglycemia might cause harm.[36,37] Finally, the 2008 NICE SUGAR (Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation) trial applied the Leuven protocol to more than 6000 patients and demonstrated that, if anything, tight glycemic control may worsen outcomes in critical care,[38] likely as a result of hypoglycemia.[39] Although the IIT episode contains many lessons, it remains a textbook demonstration of the difference between inflammation (e.g., the response to surgery, especially when cardiopulmonary bypass is involved) and critical illness, which was more likely to be represented in the population from the Leuven Medical ICU and the multicenter trials. Importantly, the mortality of untreated patients in the Leuven Surgical ICU was about 8%,[34]

whereas that of the same group in the Leuven Medical ICU was 40%,[35] which clearly demonstrated that they were different.

- *Monitoring the heart*: The widely held belief that there is a need to monitor substrate delivery to tissues has led to the development of a wide variety of hemodynamic monitoring devices. Conventional monitoring of the circulation involves using heart rate (HR), mean arterial pressure (MAP), urinary output, and CVP. The optimal MAP is unknown.[40,41] CVP does not measure volume responsiveness,[42] and high CVPs have been associated with adverse outcomes.[43] More important, the meaning of a change in CVP is entirely dependent on the model of cardiovascular function used. A rise in CVP in the Frank-Starling formulation of cardiac function (which focuses on the determinants of ventricular output), where it serves as a surrogate for preload, should result in an increased stroke volume (SV).[44] However, in the Guyton model, where the focus in on ventricular filling, a similar increase in CVP will reduce the gradient for flow into the ventricle and thus will decrease SV.[45] The "normal" urinary output of more than 0.5 mL/kg/hr is actually a "minimum" hourly output and is based on theoretic calculations involving the maximal capacity to concentrate the urine and the "average" daily nitrogen load to be eliminated. There are many reasons why these numbers may not be germane either in individual patients or in the setting of either stress or critical illness. Importantly, there are no studies demonstrating that achieving this target affects the development of renal injuries.

One way in which to more accurately monitor cardiac function is to directly measure the effects of a change in volume on cardiac output (or to eliminate the effects of HR on SV).[46] For two decades, pulmonary artery catheters (PACs) were extensively used to monitor both perioperative and critically ill patients. Use has declined because a large randomized trial of PACs in ICUs failed to demonstrate a mortality benefit.[47] However, this study was performed on approximately 2000 patients undergoing high-risk surgery; the overall mortality was under 8%, likely too low to be an appropriate endpoint. Given the nature of the patient population and the low mortality, it is likely that many of the patients entered into this trial were not critically ill.

Parenthetically, the incidence of renal insufficiency in the PAC group was 7.4%, whereas it was 9.8% in the standard care group, generating a *P* value of .07, just above the threshold for significance. Indeed, if one more patient in the standard care group had developed renal insufficiency, or one less patient in the PAC group had not, the use of PACs might have increased.

In summary, it is imperative that critical care practitioners do not confuse inflammation and critical illness. Examples of the dangers inherent in failure to account for these differences, beyond those detailed here, abound. Both may require enhanced surveillance and intensive monitoring, but the need for intervention and, if necessary, the time course during which intervention is required are likely to be different. Inappropriately applied therapy is both expensive and potentially dangerous.

AUTHORS' RECOMMENDATIONS

- Not all patients in ICUs are critically ill; patients admitted after surgery or for monitoring may need to be managed differently than critically ill patients.
- Research data derived from the perioperative (including surgical ICUs) literature may not be applicable in critical illness.
- The perioperative realm provides a useful laboratory for new therapies or monitors; however, it is characterized by a controlled and curtailed stress response, recovery from which is predictable.
- Acute critical illness is characterized by organ dysfunction.
- Persistent critical illness likely reflects an underlying disease process that is different from either stress or acute critical illness, and interventions designed for one may be ineffective or even harmful in the other.

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